

undetectable allergen protein content in the seed. Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

Applicants assert that the present specification provides enabling support for a person of ordinary skill in the art to make and use the claimed method. Specifically, on pages 45-52 of the application, methods are disclosed for preparing the contemplated polynucleotide and cloning the polynucleotide in the antisense orientation into a vector optimized for peanut transformation. Methods of plant transformation are well known in the art and the specification teaches several methods for transforming a recipient peanut plant cell (see pages 57-58). The instant application teaches regenerating a peanut plant from the transformed cell (pages 58-59) and identifying transgenic peanut plants with reduced or undetectable allergen content (pages 58-61). Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

State of the art and unpredictability of the art

The Examiner alleges that at the time the invention was made antisense gene suppression was unpredictable and therefore the claimed invention cannot be enabled. Specifically, the Examiner cites the teachings of Shewry et al.(2001), Metcalfe et al.(1996), and Branch (1998) to evidence unpredictability in the field of antisense control of gene expression in plants. Applicants traverse and respectfully request reconsideration and withdrawal of the rejection.

Applicants submit that the Examiner has improperly cited Shewry et al. (2001). Applicant's filing date is November 20, 2000 and the present application claims priority to U.S. Application 60/167,255, filed November 19, 1999. Therefore, the citation of Shewry et al. (2001) is invalid and all issues therefrom are made moot.

Applicants assert that at the time the invention was made antisense technology was a well-established and utilized tool for suppression of gene expression in plants. Furthermore, Applicants contend that the Examiner has failed to provide evidence supporting the alleged unpredictability of antisense technology for reducing gene expression in plants. For example, and as cited and acknowledged by the Examiner, Tada et al. (1996) teaches a method for

antisense suppression of a 16 kDa allergen in rice seeds. Based on the teachings cited by the Examiner, the Examiner has admitted that antisense was an established technology at the time the invention was made to reduce gene expression in plants. Accordingly, Applicants submit that the specification of the instant invention is enabled for the production of transgenic peanut plants with reduced levels of allergen proteins

Applicants contend that the Examiner's argument for lack of enablement conflicts directly with the Examiner's obviousness argument. For example, on page 6 of the November 6, 2002 Office Action, the Examiner comments that "[t]he unpredictability of the art of antisense in general adds to the lack of enablement for the current invention...." Yet, on page 10 of the Office Action, the Examiner asserts that "[i]t would have been obvious to one of ordinary skill in the art to devise a method for producing transgenic peanut plants with reduced or undetectable allergen protein content in the seed...." The Examiner further comments on page 11 that "[o]ne of ordinary skill in the art would have expected to be successful in cloning the promoter-linked homologous region in a vector and transforming a cell with that vector since Tada et al. taught such methods would successfully reduce allergen protein content in seeds." Based on the teachings cited by the Examiner in support of obviousness rejections, the Examiner has admitted that antisense was available at the time the invention was made to reduce gene expression in plants. Moreover, Applicants submit that the specification of the instant invention is enabled for the production of transgenic peanut plants with reduced levels of allergen proteins.

In support of the Examiner's argument that antisense technology is unpredictable, the Examiner asserts that the long-term stability of antisense technology is not well established and that the reversion of antisense technology could have serious implications, particularly for the reversion of genes encoding allergens. Applicants contend that the Examiner has failed to provide evidence supporting the alleged reversion of antisense genes. Furthermore, Applicants submit that the present invention provides for the use of a *gene fragment*, as opposed to a full length sequence, that corresponds to a homologous region common to more than one *Ara h* allergen gene. Consequently, even if reversion could occur, a full length protein would not be produced.

Issues under undue experimentation

The Examiner asserts that one of ordinary skill in the art at the time the invention was made would have been required to perform undue trial and error experimentation to practice the current invention. Specifically, the Examiner comments that experimentation beyond which is taught in the specification would be required to produce a transgenic peanut plant with reduced or undetectable allergen protein content. Applicants respectfully traverse.

Applicants assert that the specification provides full disclosure for one of ordinary skill in the art to produce a transgenic peanut plant with reduced or undetectable allergen protein content in the seed. In particular, the specification discloses methods for identifying a homologous region common to more than one *Ara h* allergen gene, cloning the nucleotide sequence in a vector modified for peanut transformation, transforming a recipient peanut cell with the vector, and identifying and selecting fertile peanut plants that produce seeds with reduced or undetectable allergen protein content. While Applicants concede that not all of the transgenic plants produced by the inventive methods may contain seeds with reduced or undetectable allergen protein content, the specification clearly teaches the selection and identification of plants containing seeds with reduced or undetectable allergen protein content. For example, on page 60, the specification teaches use of northern blots hybridized with radio-labeled probes to identify and select transgenic plants. Additionally, on page 60, the specification teaches use of ELISA to detect allergen levels in transgenic peanut plants. Thus, a skilled artisan would be able to identify and select plants with reduced allergen content with ease.

The Examiner is directed to Example (B) of MPEP § 2164.06 (b) wherein it was established that the steps of screening and selecting monoclonal antibodies for a desired phenotype, while tedious and laborious, neither constitutes undue experimentation nor renders the specification non-enabling. “The nature of monoclonal antibody technology is such that the experiments first involve the entire attempt to make monoclonal hybridomas to determine which ones secrete antibody with the desired characteristic. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). It follows, therefore, that screening and

selecting transgenic peanut plants with reduced levels of allergens does not constitute undue experimentation.

The fact that some experimentation may be necessary to make or use the invention does not render the specification non-enabling. It is well established that “an extended period of experimentation may not be undue if the skilled artisan is provided sufficient direction or guidance.” *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). Moreover, it has been argued that “...a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Applicants assert that the specification discloses clearly how to identify and select transgenic peanut plants and that such selection analyses are not only well-known, but routine, to one of skill in the art.

For the reasons set forth above, Applicants respectfully request that the Examiner withdraw the rejection of claims as non-enabled.

Rejections under 35 U.S.C. §103

Claim 21 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Tada et al.(1996) in view of Kleber-Janke et al. (1999). Applicants respectfully traverse and request reconsideration and withdrawal of the rejection.

The Examiner’s rejection of claim 21 as being unpatentable over Tada et al.(1996) in view of Kleber-Janke et al. (1999) is flawed because the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the combination of the prior art references must teach or suggest all of the claim limitations. The present rejection is flawed because the combination of the prior art references does not teach or suggest all of the claim limitations.

Tada et al. teaches a method for antisense suppression of a 16 kDa allergen in rice seeds. Specifically, Tada et al. teach operably linking a fragment of the cDNA encoding the 16 kDa rice allergen in the antisense orientation and cloning the fusion construct into a vector for rice transformation. The teachings of Tada et al. demonstrate that antisense RNA markedly reduced the mRNA and protein content of the 16 kDa allergen in transgenic rice seeds.

The Examiner asserts that Tada et al. teaches that the antisense approach could be used in other crop plants containing known allergens, such as peanuts and soybeans, to selectively reduce or eliminate the levels of specific allergenic proteins. Upon review of Tada et al., Applicants submit that Tada et al. neither teaches nor suggests that the antisense suppression of gene expression could be used in other crop plants, such as peanuts and soybeans. Tada et al. teaches antisense suppression specific to rice plants.

Applicants, however, agree with the Examiner's assessment that Tada et al. fails to teach the *Ara h* gene or methods of identifying a homologous region common to more than one *Ara h* gene. Since Tada et al. fails to teach the use of antisense technology in other crop plants or the use of homologous *Ara h* regions for antisense transformation, it follows, therefore, that the teachings of Tada et al. do not anticipate the methods of the present invention.

Kleber-Janke et al. teaches the isolation and characterization of IgE-binding proteins of peanuts. The Examiner asserts that Kleber-Janke et al. teach the alignment of the amino acid sequences of *Ara h*2, *Ara h*6, and *Ara h*7. While Kleber-Janke et al. discloses the amino acid homology between *Ara h*2, *Ara h*6, and *Ara h*7, Kleber-Janke et al. fails to teach the amino acid homology between *Ara h*1, *Ara h*2, *Ara h*3, *Ara h*4, *Ara h*5, *Ara h*6, and *Ara h*7. Furthermore, Kleber-Janke et al. fails to teach or suggest the method of identifying and selecting a region homologous to *Ara h*1, *Ara h*2, *Ara h*3, *Ara h*4, *Ara h*5, *Ara h*6, and *Ara h*7. Finally, Kleber-Janke et al. neither teaches nor suggests operably linking the homologous region in the antisense orientation to a promoter, cloning the promoter-gene construct in a vector modified for peanut transformation, transforming a recipient peanut cell with the vector, and identifying and selecting fertile peanut plants that produce seeds with reduced or

undetectable allergen protein content. It follows, therefore, that the teachings of Kleber-Janke et al. fails to teach or suggest the inventive methods of the present application.

The combination of the teachings of Kleber-Janke et al. with Tada et al. does not cure the deficiencies of Tada et al. Kleber-Janke et al. fails to teach or suggest the method of identifying and selecting a region homologous to *Ara h1*, *Ara h2*, *Ara h3*, *Ara h4*, *Ara h5*, *Ara h6*, and *Ara h7*. Moreover, Kleber-Janke et al. neither teaches nor suggests operably linking the homologous region in the antisense orientation to a promoter, cloning the promoter-gene construct in a vector modified for peanut transformation, transforming a recipient peanut cell with the vector, and identifying and selecting fertile peanut plants that produce seeds with reduced or undetectable allergen protein content. Therefore, the present invention is not obvious over Tada et al. in view of Kleber-Janke et al.

It is well-settled that obviousness under 35 U.S.C. §103 cannot be established by combining the teachings of the prior art to obtain the claimed invention, absent some teaching, suggestion, or incentive supporting the combination. The Examiners asserts that one of ordinary skill would have been motivated to combine the teachings of Tada et al. with the teachings of Kleber-Janke et al. Applicants submit that it would not have been obvious to one of ordinary skill in the art to identify a homologous region common to more than one *Ara h* allergen gene. Furthermore, it would not have been obvious to place this homologous region in the antisense orientation and clone it in a vector suitable for the transformation of peanut cells.

Additionally, Applicants submit that an obviousness rejection of the claimed invention may not be based upon unqualified hindsight reasoning. It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the cited art so that the claimed invention is rendered obvious. It is well established that "[O]bviousness can not be established by hindsight combination to produce the claimed invention." *In re Gorman* 933 F.2d 982, 986, 18 USPQ 2d 1885, 1888 (Fed. Cir. 1991).

Applicants submit that one of ordinary skill would not have been motivated to combine the teachings of the cited art. Furthermore, even if there was motivation to combine

the teachings of Tada et al. with Kleber-Janke et al., the combination of references would not provide for all the features of the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If there are any questions concerning this application, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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